REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Claims 3 and 4 have been amended in conformance with U.S. practice. In response to the Examiner's question, the Applicant confirms that the term "ameliorant" in claims 3 and 4 means the compound 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof.

In reply to the Examiner's question, the Applicant confirms that the compound and its acid addition salt have the high binding affinity for a serotonin receptor 4 ($5HT_4$).

In reply to the ground of rejection that claim 3 recites "does not cause arteritis and thrombus formation", claim 3 has been amended to recite "does not cause arteritis or thrombus formation".

In view of the foregoing, the rejection of claims 3 and 4 under 35 USC 112, second paragraph, as being indefinite is deemed to be overcome.

Claims 3 and 4 are rejected under 35 USC 102 as anticipated by or, in the alternative, under 35 USC 103 as obvious over Fujiwara et al., USP 5,143,935. This ground of rejection is respectfully traversed.

The present invention is characterized by administering 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof (hereinafter referred to as the "present compound"), which has high binding affinity for a serotonin receptor 4 ($5HT_4$) and does not cause thrombus formation, arteritis or encephalomalacia, and has an effect of improving the movement of the digestive tract.

The present compound is optically active, because the chiral centers of the 2 and 4 positions in the pyrrolidine ring have a (2S,4S)-configuration.

It had been known in USP 5,143,935 and JP-A-17434/1993 that 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide (hereinafter referred to as "TKS159"), or an acid addition salt thereof has an effect of improving the movement of the digestive tract. Although the present inventors tried to develop TKS159 as a medicine, the disorders such as thrombus formation, arteritis or encephalomalacia (please see Reference

Example on page 28, penultimate line to page 30, line 12 in the specification) were observed when TKS159 was orally administered repeatedly in a safety test using a beagle dog.

As a result, it was judged that TKS159 was not suitable as a pharmaceutical for humans. Under these circumstances, the present inventors have made extensive studies, and finally they have surprisingly found out that the present compound which is one metabolite in a beagle dog does not cause thrombus formation, arteritis or encephalomalacia, and has high binding affinity for a serotonin receptor 4 ($5HT_4$), and shows the excellent effect of improving the movement of the digestive tract (please see the disclosure on page 2, line 1 to page 3, line 8 in the specification).

Fujiwara discloses in Example 10 on column 5, 4-amino-5-chloro-2-methoxy-N-(5-hydroxymethyl pyrrolidin 3-yl)benzamide hydrochloride. Also, Fujiwara discloses 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4- pyrrolidinyl)benzamide hydrochloride (claim 3 and column 14, lines 22-24).

However, optically active 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethy1-4-pyrrolidinyl]benzamide or an acid addition salt thereof, which is used in the methods of the present invention, is not concretely disclosed in the cited Fujiwara.

Further, Fujiwara describes on column 1, lines 36-39 that "a novel class of the compounds having no or substantially no activity toward central nervous system, and having an excellent promoting activity to digestive tract, especially to stomach" is provided. Tables 1 and 2 on column 14, lines 32-64 show the promoting rate (%) of stomach excretion in mouse, and the prevention of vomiting in dog.

However, a benzamide derivative having no adverse cardiovascular effects, and having high binding affinity for a serotonin receptor 4 ($5HT_4$) is neither described nor suggested in Fujiwara.

Moreover, the Applicant respectfully disagrees that the reference teaches a small genus of compounds such as contained in *In re Schaumann* cited by the Examiner.

In Schaumann, the prior art disclosed 14 compounds, later further narrowed to 7, considering express preferences. Additionally, the structural formula of this prior art contained a single variable. The single variable, R, was defined in claim 1 as "a lower alkyl radical" and that expression was defined in the specification as the specific group contained in the compound of Schaumann. Thus the prior art specifically taught the compound of Schaumann.

In contrast, the instant Fujiwara reference teaches a compound having two variables. Variable 1 is R_1 which is a hydrogen atom, lower alkyl, halogen substituted lower alkyl or aralkyl group. The second variable are R_2 is hydrogen or a lower alkyl. The instant reference does not define "lower alkyl" or "halogen substituted lower alkyl or aralkyl group". Therefore it is difficult to estimate the exact number of compounds encompassed by the reference teachings. Nevertheless, it is clear that the instant reference teaches far more than 14 compounds taught in Schaumann.

Accordingly, the cited reference fails to anticipate the methods of claims 3 and 4, because the cited reference fails to disclose explicitly or inherently the specific compound recited in the claims.

The present invention is based on the findings of the problems to be solved in that TKS159, which is a specifically claimed compound in Fujiwara, causes adverse cardiovascular effects, such as thrombus formation, arteritis or encephalomalacia (please see Reference Example on page 28, penultimate line to page 30, line 12 in the specification).

Fujiwara neither describes nor suggests the problems to be solved by the present invention, namely occurrence of cardiovascular adverse effects, such as thrombus formation, arteritis or encephalomalacia. Furthermore, as mentioned above, Fujiwara neither discloses nor suggests a benzaminde derivatives having no cardiovascular adverse effects such as thrombus formation, arteritis or encephalomalacia, and having high binding affinity for a serotonin receptor 4 ($5HT_4$).

It is clear from Working Examples 10 to 12 (pages 25-27) in the present specification that the present compound has no cardiovascular adverse effects such as thrombus formation, arteritis or encephalomalacia, A summary of Working Examples 10 to 12 is set forth below.

Example 10

· Test compound: 4-amino-5-chloro-2-methoxy-N-[(28,4S)-2- hydroxymethy1-4-pyrrolidinyl]benzamide (hereinafter referred to as TM161) monohydrochloride

· Test animal: three beagle dogs

· Conditions of administration :

Orally at a dose of 100 mg/kg, once a day for 4 weeks

· Results:

Pathohistological test on the sections was performed using a light microscope. Abnormality was not seen in any organ with the naked eye. Abnormality was not seen also in a pathohistological test, and encephalomalacia, arteritis and thrombus formation were not recognized.

Example 11

· Test compound: TM161 monohydrochloride

· Test animal:

Five Sprague-Dawley male rats, 4 weeks old, weighing each 160.3 to 169.5 g

· Conditions of Administration:

The rats were grouped into four groups of a control group, a 300 mg/kg administration, a 1000 mg/kg administration, and a 2000 mg/kg administration

One-time dose is 10 ml/kg, and the specimen was forcibly administered orally at 9 o'clock to 12 o'clock for 28 days once a day.

· Results:

An organ and a tissue such as brain, heart, aorta, lung, pancreas, liver, and cava were observed with the naked eye and histologically, and subjected to a pathohistological test.
Abnormality was not seen with the naked eye in any organ. In addition, also in a pathohistological test, abnormality was not seen, and encephalomalacia, arteritis and thrombus formation were not recognized.

Example 12

· Test compound:

TM161 monohydrochloride and TKS159 monohydrochloride

· Test animal: A Wister male rat

· Test method:

An esophagus in a chest cavity was extracted from a Wister male rat. The muscularis propria sample containing longitudinal muscle and circular muscle was removed to prepare a muscularis mucosae sample having a length of about 2 cm. Each 1 μM of methysergide, ketanserin and granisetron were added. TM161 monohydrochloride was accumulatively applied at a common

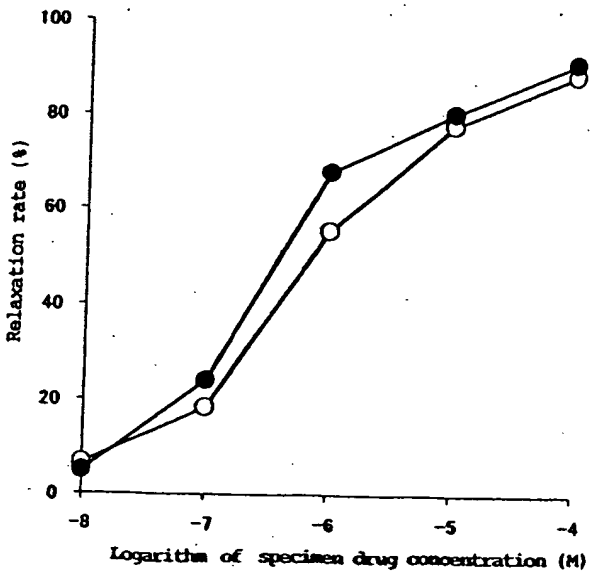
ratio of 3 after 30 minutes, and a degree of relaxation was isotonically (stationary tension; about 0.5 g) measured via a transducer.

Separately, the same procedure was also performed regarding TKS159 hydrochloride, and an intensity of the action was compared.

Results;

EC_{50} of TM161 hydrochloride is 0.7 μM, which is lower than 1.1 μM of EC_{50} of TKS159 hydrochloride.

(Please see Fig. 3 in the specification which is reproduced below)



● is TM161 hydrochloride

Further, it is clear from Working Example 1 (page 18, line 27 to page 19, line 17) in the present specification that the present compound has high binding affinity for a serotonin receptor 4 ($5HT_4$).

Example 1

Measurement of action of TM161 monohydrochloride on serotonin receptor 4:

IC_{50} of TM161 monohydrochloride is 0.25 μM, which is lower than 0.45 μM of IC_{50} of TKS159 hydrochloride. This means that affinity of TM161 monohydrochloride for a serotonin receptor 4 is stronger compared with affinity of TKS159 hydrochloride.
(Please see also Fig. 1 and brief description of the drawings on page 8, lines 12-24 in the specification)

There is submitted herewith a Rule 132 Declaration executed by Dr. Toshiharu Yanagi, one of the present inventors. The Declaration contains Experiments 1 to 5. The relationship between the Experiment Nos. of the Declaration and the Example Nos. in the present specification is shown below.

The Rule 132 Declaration Experiment No.	The present specification Example No.
1 (1)	3
|	|
1 (7)	9
2	1
3	10
4	11
5	12

In view of the foregoing, it is respectfully submitted that the claimed methods as amended are neither anticipated by nor obvious from the teachings of the cited reference. The cited reference fails to disclose or suggest the unexpected effectiveness and absence of adverse cardiovascular side effects of the prior art.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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